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CONCERNING THE MUTATION THEORY

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THE mutation theory of evolution has met with a stormy reception, despite the fact that De Vries, and most of its supporters, have avowed themselves adherents of the doctrine of natural selection. Some of the older followers of Darwin have insisted that the large steps, which they still believe are the only kind that the mutation theory postulates, could not give the small continuous stages through which evolutionary changes take place. Now, the mutation theory has never made any such "large" claims. On the contrary, it has been pointed out repeatedly that the mutational changes may be extremely small. The theory does claim that the genetic factors are discontinuous, although the characters that they stand for may or may not be discontinuous. De Vries himself has said in the "Mutation Theory" (Vol I, page 55): "Many mutations are smaller than the differences between extreme variants," meaning by the latter term fluctuating variations, pointing out by way of illustration that the constant species of *Draba verna* "differ less from each other than do extreme variations in the same characters." While De Vries's work on the evening primrose, *Œnothera Lamarckiana,* is generally conceded to be the starting point of the modern mutation theory, nevertheless, the peculiar way in which Lamarck's primrose produces its new and recurrent types, which De Vries regarded as the real mutative process, has been difficult to harmonize with the way in which practically all other forms give rise to mutants.

The genetic behavior of the evening primrose is so well known that it is superfluous to describe it here in detail, especially since we are, for the moment, more concerned with the critical treatment of the results than with their exposition. It

will suffice to recall that De Vries found an escaped European garden plant known as *Œnothera Lamarckiana* that produced new types in sufficient numbers to furnish numerical data of unusual value. Some of these new types bred true, although some of them continued to give further evidence of "mutation." Immediately the question arose: Is *O. Lamarckiana* a wild species, or a product of hybridization; and if the latter, is not its mutation process only the resolution of the hybrid into its components? The search for the wild type in America led practically to failure, but the search led to the important discovery that other wild species of the same and related genera were also mutating. Into the vexed question as to whether most or all wild types may not themselves be hybrids, it is not necessary to enter here; for if the point of view that I wish to present is correct, the behavior of *O. Lamarckiana* would be outwardly nearly the same whether it arose by the union of two species, each bearing lethals, or whether its present "balanced lethal" condition arose within the plant itself, no matter what its origin may have been.

That the situation in *Œnothera* is complicated will be clear, I think, to any one who has followed De Vries's latest work "Gruppenweise Artbildung," Davis's experiments with forced germination, Geerts, Gates and Lutz in their cytological work, Stomps and Bartlett on mutability in other species of the genus, MacDougal, Heribert-Nilsson, G. H. Shull and Honing in their analytical work on the genetics of *Œnothera*.

Recently a case apparently similar to the mutation phenomenon of *Œnothera* has been worked out on the fruit fly, *Drosophila melanogaster*, by Dr. H. J. Muller, which, I venture to think, gives us the clue that we have needed so long to show what takes place in Lamarck's evening primrose when it throws off, in definite percentages, characteristic mutant types. This evidence makes it not improbable that this type of behavior of *Œnothera* may be due to the presence in it of *lethal* factors, so closely linked with recessive factors, that only when the linkage is broken do the recessive factors come to light. Here we have a remarkable situation, one that would have seemed, *a priori*, highly improbable, but now that we can at will make up stocks that give the same kind of results as does *Œnothera* the behavior of this plant can be brought into line with mutation, as seen in other animals and plants.

The history of the discovery of a balanced lethal stock in *Drosophila* and its interpretation by Muller is as follows: An

early observed mutant of the fruit fly, *Drosophila* had Beaded wings. Beaded stock was bred for several years, and persisted in throwing some normal offspring. Selection produced no advance until suddenly a time came when Beaded no longer threw any normals; or so few as to be negligible. Why had it not been possible to make pure the stock in the first instance? And what happened when it became pure?

Muller took up the work at this stage and has solved the problem as follows: He found that the factor for Beaded is dominant for wing character, but lethal in double dose. As in the case of the yellow mouse, only the hybrid (heterozygous) combination exists, and consequently when two Beaded flies mate they produce two Beaded to one normal fly, as shown in Fig. 1. Here the first pair of vertical lines stand for the pair of third chromosomes present in the egg before its reduction. The two factors here involved, that for Beaded and its allelomorph for normal, are indicated at the lower end of the vertical lines. The two corresponding chromosomes in the male are represented to the right of the last. After the ripening of the germ cells each egg and each sperm carries one or the other

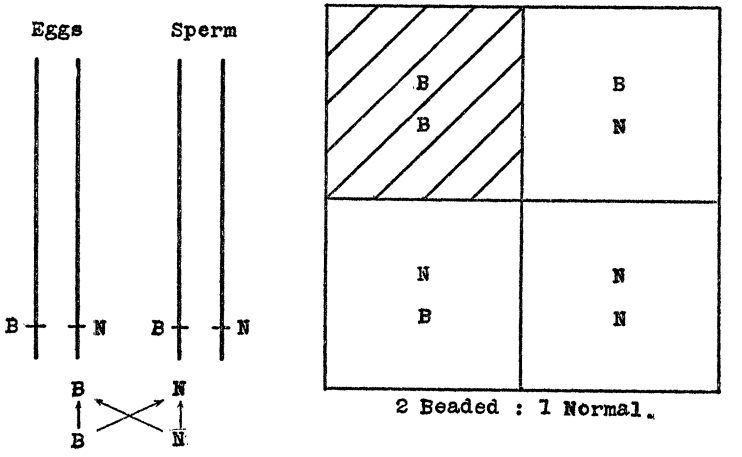


FIG. 1.

of these chromosomes. Chance meetings of egg and sperm are indicated by the arrow-scheme below in the figure, which gives the combinations (classes) included in the four squares. The double dominant BB is the class that does not come through. The result is two Beaded (heterozygous) to one normal fly.

The Beaded stock remained in this condition for a long time; although selected in every generation for Beaded, it did

not improve, but continued to throw 33 per cent. of normal flies. Then it changed and bred nearly true.

The change must have been due to the appearance of another lethal factor (now called lethal three or l_1 in the diagram), because a gene for such a lethal was found in the race when studied later by Muller. The lethal factor is recessive; it is fatal when in double dose. It behaves as do other lethals which Bridges and Sturtevant especially have demonstrated to be frequently present in *Drosophila*. In fact, lethal factors appear to be the commonest type of mutation, which is not surprising when one recalls that most of the mutants are deficient types, whose defects, carried a step further, would in many cases be fatal to the individual. It is only in this sense that the term lethal factors is used by us. They are not supposed to be poisons or any special kind of modification, but only factors that cause some structural or physiological change of such a sort that the individual does not begin its development, or, if it does, it perishes somewhere along the road. In fact, we have lethals that affect the egg stages, the larval and pupal stages, the newly hatched flies, and semi-lethals that weaken the adults, although they do not necessarily kill.

The lethal gene that appeared in the Beaded stock was also in the third chromosome, and in the chromosome that is the mate of the one carrying the gene of a Beaded, *i. e.*, in the *normal* third chromosome of the Beaded stock. The lethal gene lies so near to the level of the Beaded-normal pair of genes that almost no crossing-over takes place between the levels occupied by the two pairs. These relations are illus-

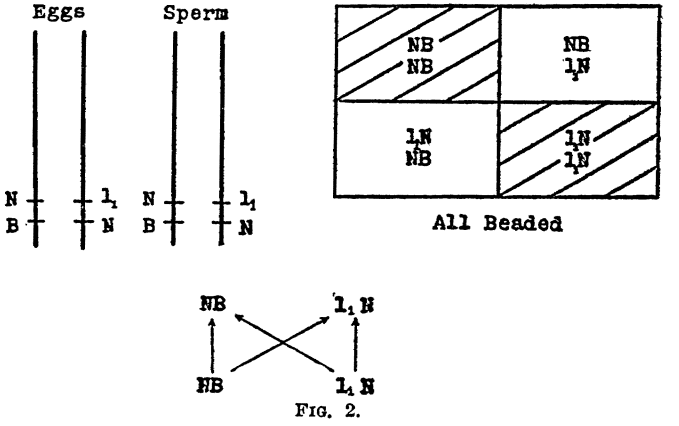


FIG. 2.

trated in the next diagram, Fig. 2. Here again the two pairs

of vertical lines to the left represent the two third-chromosome pairs in the female and to the right the male. The location of the two pairs of genes involved, N — l_1 and B — N, are indicated. These combinations give the four classes in the squares, of which two classes die, viz., NNBB (pure for Beaded) and $l_1 l_1$NN (pure for lethal three). The result is that only Beaded flies come through, and since all these are heterozygous both for B, and for l_1 the process is self-perpetuating.

If the preceding account represented all of the facts in the case, the stock of Beaded should have bred perfectly true, but it has been shown in *Drosophila* that crossing-over between the members of the pairs of genes takes place in the female. Hence we should expect a complication due to crossing-over here unless the level of the two pairs of genes was so nearly the same as to preclude this possibility. In fact, in addition to the Beaded flies the stock in this condition would give 10 per cent. of crossing-over, *i. e.*, it would still produce a small percentage of normal flies. It so happened, however, that there was present in the stock a third gene that lowers the amount of crossing-over in the female to such an extent that, for the two "distances" here involved, practically none takes place. When it does a normal fly appears, but this is so seldom that such an occurrence, if it happened in a domesticated form of which the wild type was unknown would be set down as a mutation like that shown by the evening primrose.

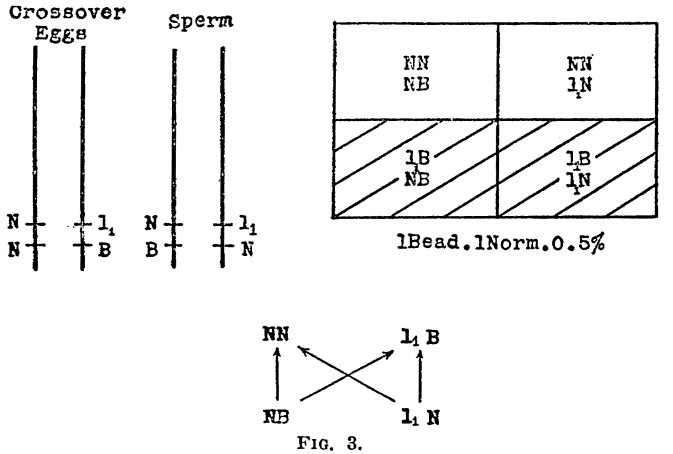


FIG. 3.

The third factor that enters into the result is not unique, for Sturtevant has shown that crossover factors are not uncommon in *Drosophila*. The analysis that Muller has given for

Beaded, while theoretical, is backed up by the same genetic evidence that is accepted in all Mendelian work. It makes an assumption that can be demonstrated by any one who will make the necessary tests. Lest it appear, however, that this is a special case depending upon a very unusual situation, let me hasten to add that with the material that we have in hand it is possible to produce at will other balanced lethal stocks that will "mutate" in the sense that they will throw off a small predictable number of a mutant type—a type that we can introduce into the stock for the express purpose of recovering it by an apparent mutation process.

Dichete is a third chromosome dominant wing and bristle character and like Beaded a recessive lethal. In a certain experiment flies with the gene for Dichete in one of the third chromosomes and with a gene for the recessive eye color peach in the other were inbred for several generations. A lethal appeared by mutation in the peach-bearing chromosome very near the level of the Dichete gene in the opposite chromosome.

The order of these genes is shown in Fig. 4. This is then a

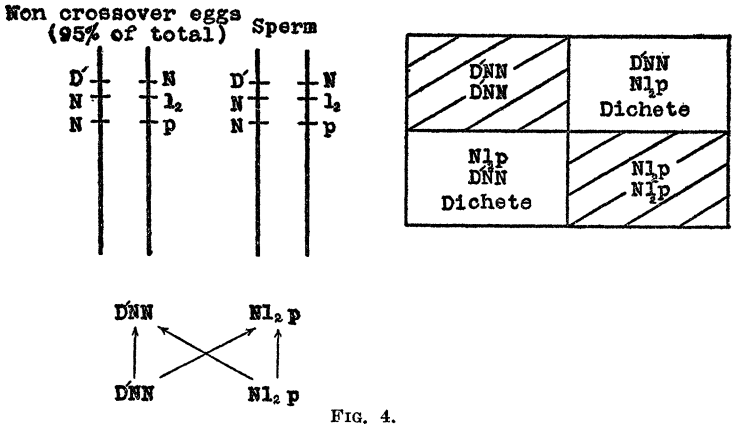


FIG. 4.

balanced lethal stock that throws only Dichete flies,[1] except for a small percentage of Dichete peach flies due to crossing-over. The result for the non-crossover classes is shown in the next figure, Fig. 5. Only two of the four classes come through; the two that die are the one pure for Dichete and the one pure for lethal. The surviving classes continue to produce the same kind of offspring since they are, like the parents, heterozygous for the two lethal factors. But the factors are not near enough together to prevent crossing-over. This occurs in about 5 per

[1] Very rarely a crossover not—Dichete fly will appear.

cent. of cases between the lethal and peach genes. The next diagram, Fig. 5, shows how when crossing-over takes place in

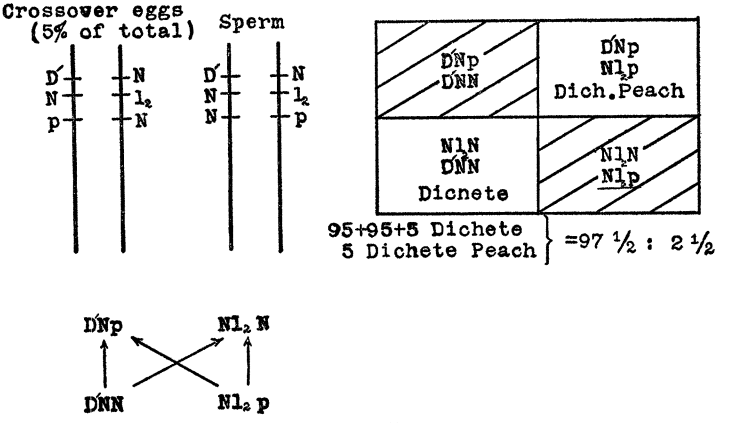


FIG. 5.

the female, there result (see squares) four classes of which two die (as before), and of the two that survive one is Dichete peach. Taking both non-crossover and crossover results together, the expectation is $95 + 95 + 5$ Dichete to 5 Dichete peach or 97½ to 2½. This stock then breeds true for Dichete without showing the gene it carries for peach eye color except in a small percentage of cases, and if the peach-eyed fly should be unable to establish itself in nature, like some of the *Œnothera* mutants, the stock would not be changed by it, but continue to throw off a few "mutants" with peach-colored eyes.

Now this process is not what is ordinarily meant by mutation, for we mean by the latter that a new type has suddenly arisen in the sense that some change has taken place in the germ plasm—a new gene has been formed. The process here described is one of recombination of genes shown by Mendelian hybrids, the only unusual feature that all the phenomena involved do not come to the surface because many classes are destroyed by lethals.

The results are interesting also in another way. It has been assumed by those who think that *O. Lamarckiana* is a hybrid that the mutant types are only the segregation products of the types or combinations that went in to produce the hybrid. But the *Drosophila* cases show that balanced lethal stocks may arise within stocks themselves by the appearance in them of lethal factors closely linked to other factors—new or old ones. When new genes arise in such lethal stocks the process may be

one of true mutation, but the revelation of the presence of the gene is hindered by the lethal factors, so that when the *character* appears, it appears in a much smaller number of individuals than would be expected for a "free" mutant due to recombination of mutant genes that had arisen in an earlier generation. As a matter of fact, the first appearance of even ordinary mutants, unless they be dominant, must come two or more generations after the mutation has taken place, for the evidence indicates that mutation appears in only one chromosome at a time.[2] In the case of sex-linked genes, however, any mutation that takes place in one of the X-chromosomes of the mother is revealed if the egg containing it gives rise to a son, because he has but one X-chromosome and that comes from his mother.

The delayed occurrence then of mutants in balanced stocks is not different from the delay in other stocks,—only when the recombinations occur in balanced lethal stocks they must have been preceded by crossing-over which diminishes the number of mutants that appears. The number of mutants that appears is determined by the distance of the genes for the character from the nearest lethal gene.

One of the most interesting features of the evening primrose arises when it is bred to certain other species or varieties. It gives rise to two kinds of offspring called Twin Hybrids, to one pair of which De Vries gives the names *læta* and *velutina*. Now it is a feature of balanced lethal stocks like Beaded that

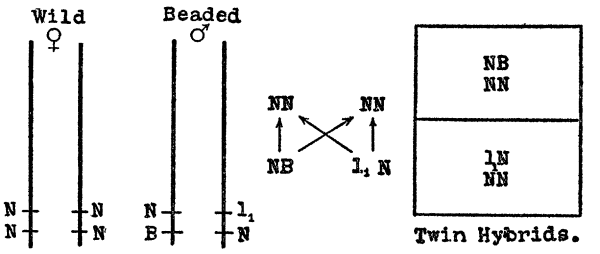
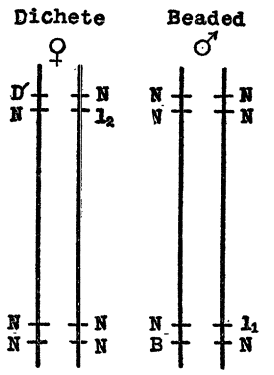


FIG. 6.

they repeat precisely this phenomenon. For instance, if a Beaded male is crossed to wild female, two kinds of offspring are produced, viz., Beaded and normal. A similar process would account for twin hybrids in *Œnothera* crosses. There is another peculiar phenomenon that has been described for

[2] If in self-fertilizing forms a mutation takes place far back in the germ plasm the new character might appear at once.

crosses in the evening primroses, viz., the occurrence in F_1 of four types. This phenomenon, too, can be imitated in *Drosophila* by crossing balanced lethal Dichete to balanced lethal Beaded (Fig. 7).



Both stocks breed true

D N N N N N N B Bead.Dichete	D N N N N N l_1 N Dichete
N l_2 N N N N N B Beaded	N l_2 N N N N l_1 N Normal

Four types in F_1 1:1:1:1

FIG. 7.

Other parallels might be cited, but these, I think, will suffice to indicate very strongly that the discovery of balanced lethal stocks may solve the outstanding difficulty of mutation and inheritance in *Œnothera* and bring it into line with other groups. There are, of course, other peculiarities of the evening primrose that such zygotic lethals will not explain; such, for instance, as the 15-chromosome type; and *O. gigas*. But these cases are already on the road to solution.

The occurrence of other lethals, called *gametic* lethals, that kill the germ cells—gametes—before they are ready for fertilization, has already been invoked by De Vries and others to explain the peculiarity of double reciprocal hybrids. As *Drosophila* has not shown any *gametic* lethals, we have no such parallel to this case, but confirmatory evidence has been found in other cases, as in *Matthiola* (Stock), and it is not likely that De Vries's hypothesis will be seriously questioned.

If this diagnosis is correct, the "mutation" of *Œnothera* is nearer solution than ever before. Much that has been obscure is clearing up. The so-called *mutation process* in *Œnothera* has turned out to be, I venture to think, largely a phenomenon of lethals—zygotic and gametic.

Whether the genes now present in the plant arose by incorporation of mutant types by hybridizing has no longer the same interest that it had before the discovery of the phe-

nomenon of balanced lethals, because the most characteristic "mutation" process of *Œnothera* is difficult to explain even if it arose through hybridization, unless the races that entered into its composition already contained balanced lethals. In which case it is the latter relation that gives the unique feature to the *Œnothera* mutation process, and not its possible hybrid combination. On the other hand, if the lethal and mutant genes arose directly in *Lamarckiana,* its peculiar mutation behavior would be due to their presence, quite irrespective of its history. In other words, it is in either case the balanced lethal condition that gives to this plant its extraordinary propensity to throw a considerable percentage of recurrent mutant types. Possibly I am too unfamiliar with the *Œnothera* work, or too optimistic, but I can not but rejoice at the possibility of accounting for the riddle of *Œnothera* on the theory of balanced lethal factors.

Nature of the Unit of Mutation

Undoubtedly the conception of the gene as a complex organic molecule or group of molecules located in the hereditary materials is the view most easily visualized when dealing with mutational "units," but however attractive and practical such a simple notion may be, we can not afford to accept it without careful analysis of the evidence supposedly in its favor. What is this evidence?

The segregation of the members of each pair of Mendelian genes clearly leads to the idea of independent units. It would be unprofitable to discuss whether these units are material particles or dynamic centers independent of material support. Standing on a chemical basis as physiology does to-day, we may without further discussion take for granted that the genes are some sort of chemical bodies.

The evidence that these bodies are carried by the chromosomes is also on a substantial footing. This evidence has been so fully discussed in recent books and articles that it need not be taken up here.

The assortment of the different pairs of Mendelian genes has been found to be conditioned by the phenomenon of linkage which is now reasonably explained by the assumption that linked genes are those carried by the same chromosome. This interpretation is gaining ground in all fields of genetics and in my opinion has been demonstrated to be true for the chromosomes of *Drosophila.*

The linear order of the genes in the chromosomes—each chromosome containing one linear order—is the only view so far suggested that will account for all the facts relating to linkage with its associated phenomena of crossing-over and of interference.

Beyond this point conclusions become more problematical. How much or how little of the chromosome thread corresponds to a gene can at present be deduced only from the genetic evidence. Some of the possible deductions that can be drawn from this evidence seem to be the following:

So long as a stock breeds true to a given standard, in the sense that its individuals fluctuate about the same mode, the stock bears evidence to the constancy of the genes. This conclusion rests on the assumption that the differences shown by the individuals of such "pure" stock are due to differences in the environment that each has encountered in the course of its life. To prove this view to be correct required the carefully controlled experiments that Johannssen carried out with Princess beans. In this case, through long inbreeding, which its natural self-fertility ensured, the stock had become homozygous for all of its contained factors. Hence individual size difference must have been environmental and this was shown to be the case, for when the large beans and the small beans that came from the same parent were sown, the group of individuals derived from the small beans showed exactly the same distribution as the group from the large beans.

Does this demonstration of the constancy of the gene mean that the gene itself is an absolute quantity? The mutationist has sometimes been reproached on the grounds that he deduces the constancy of the gene in defiance of the plain fact that all races of animals and plants are variable, and that this variability is indeed their chief peculiarity. The answer to this supposed reproach is two-fold: First, nobody claims that Johannssen's evidence demonstrates that the gene is absolutely fixed in the sense of being quantitatively invariable; and second that the expected results for the group of individuals studied would be the same whether the gene were absolute in a quantitative sense or whether its "constancy" were due to its variability about a critical modal quantity. This point has been so little discussed and so often misunderstood that it may be well to consider it for a moment.

Let us use the term, quantitatively fixed, in the sense in which a molecule is said to be fixed. Leaving aside the finer

distinctions that might be made on the grounds that some recent work has shown that even the same chemical element may exhibit differences in its atomic weight, it will not be disputed that modern chemistry goes forward on the assumption that the molecule is a fixed quantity. If the gene is a fixed quantity in exactly this sense, results of the kind that Johannssen has found are consistently explained. But there is no evidence that conclusively establishes this view. As an alternative view the gene may be looked upon as a certain amount of material that varies about a modal amount. The amount with which the individual starts might then be supposed to influence the characters of the individual in the plus or minus direction as determined by the starting point. On the other hand, even if individuals started with slightly different quantities, the fluctuations in the amount throughout the process of cell divisions that build up the embryo might be expected to neutralize the initial difference. In other words, the assumed quantitative fluctuations of the gene in the germ-plasm stream might be expected to recur also in the body cells of the individual and "compensate," so to speak, for any variable differences at the start. Before we can hope to make any further advances along these lines it may be necessary to know more about the chemical structures of the chromatin thread and the process involved when it splits lengthwise into two daughter threads. In the meantime it is permissible to use the expression "constancy of the gene" in either sense defined above.

In the course of Mendelian work in general and more especially in connection with the clean-cut cleavage phenomenon behind Mendelian segregation the question has come up as to whether the heterozygous members of the same pair of genes may not contaminate each other either during their long residence in the same cell or in the supposedly more intimate union during the brief conjugation of the chromosome threads at synapsis. We know too little of the relation of the chromatin materials at either of these periods for any *a priori* argument to carry the slighest weight. The decision must come from the genetic evidence itself. If such a phenomenon were of general occurrence it would of course entirely obscure the whole Mendelian idea of segregation. It has not been claimed by any one in a position to weigh the evidence that contamination is general. The appeal has been made only in a few cases in order to account for supposed departures from the Mendelian process of clean separation of the genes. In not one of

these cases, so far as I know, has the evidence been convincing, and in none of them has the alternative hypothesis of modifying factors been excluded. Until such evidence is brought forward it seems more probable that the generally admitted process of clean separation of the genes is characteristic of the segregation process. How this result may at times apparently be obscured will be described later when dealing with modifying factors and also with multiple allelomorphs.

The constancy of the gene may be made to appear in a somewhat ludicrous light when a commonly accepted view of mutant genes is brought into the present connection. The presence and absence hypothesis assumes that mutation is due to loss of a factor from the original germ plasm. Taken in a literal sense the absent factor is gone, and there can be no opening for a discussion of quantitative values or of contamination. This and many other difficulties are settled once for all by presence or absence. This might, indeed, be claimed as an advantage for the hypothesis. But on the other hand, the hypothesis has never had any direct evidence to support it. It was proposed as a formal way of expressing the fact that the normal allelomorph and its partner are constant and members of a pair that segregates. Any other formulation that expresses clearly this relation explains the data as well.

It is true that there was behind the idea a form of anthropomorphism that has made a wide appeal. Many mutant characters appear as a loss when considered from the viewpoint of the original character. The great majority of the familiar mutant characters are recessive, and most of them show the character less highly developed in a sense than the same character in the wild form. For instance, white flowers and albino animals appear clearly to be due to a loss of pigment. The paler colors of several mutant races, such as thirty mutant eye colors of the fruit fly, seem less well developed than the red eye color of the wild fly. If it is legitimate to argue from the degree of development of the character to the condition of that mutant gene that stands in causal relation to it, a plausible argument may be made out for presence and absence. There are, however, not only counter arguments that have as much or as little weight according to one's personal inclinations, but in the case of multiple allelomorphs there is evidence against this interpretation, and it is important to insist, that since it is here only that we have any really critical evidence, it is hardly fair to ignore it.

The arguments against the interpretation of absence are as

follows: *First,* it is entirely illegitimate to argue from the nature of the character to the nature of the change in the germ plasm that produces the character. Theoretically it must be conceded that any change in the germ plasm should be expected to produce some change in the character or characters of the individual, and if the wild type has been brought to a high stage of development almost any change might be expected to cause a falling away from the highest condition that has been attained. But "any change" need not be a loss in the germ plasm.

Second, in order to account for dominant mutant characters the adherents of "presence and absence" feel obliged to assume a loss of an inhibiting gene, because it is difficult for them to believe that an absence could dominate a presence. There is, however, no *a priori* reason why an absence in the germ plasm might not cause a dominance in the character, for the character is, after all, only the sum total of all of the influences in the germ plasm. The concession made here by the adherents of presence and absence is interesting, however, in so far as it shows how literally they take their absences.

Other *a priori* arguments might be brought forward, but the evidence from multiple allelomorphs is so convincing that it is not necessary to discuss the hypothesis in a purely formal way. In fact, if the hypothesis were understood only as a convenient way of formulating Mendelian results the discussion would resolve itself into one of personal preference, and have no further weight; but as will be pointed out later this interpretation has been used as an attack on the mutation theory itself, for losses do not appear to be the stuff that evolution is made of. Bateson has recently developed a kind of evolutionary scheme that attributes all change to loss, shifting the problem of the origin of the genes to a remote past instead of attempting to solve the problem. It is, however, not this theoretical possibility that I referred to above, but to attacks on the mutation theory on the grounds that the mutation process is different in kind from the changes that lead to the evolution of animals and plants. This point may be next considered.

Does Mutation furnish Evolution with its Materials?

There is a predisposition on the part of systematists, paleontologists, and a few other students of "wild" types to deny that mutants are identical with the variation from which evolution obtains its materials. The reasons for their objections might repay more careful and impartial analysis than they have yet received. The chief contention that evolution has been by

means of very small changes does not require further attention, since we now know that some of the genes that are typically Mendelian in behavior produce even smaller differences than those that distinguish wild varieties and paleontological gradations. Unless such small specific and paleontological differences can be studied by the exact methods familiar to students of heredity it is not possible by inspection for any one to make any statement in regard to their hereditary behavior as Mendelian units or as not such units. By way of illustrating how difficult it may be even when genetic material is available to detect the nature of a slight change, I need only recall the fact that some of the mutant differences depend on specific modifiers that act visibly only when the chief factor so-called is itself present. Another illustration is also to the point. Owing to the many-sided effects of single genic differences the *structural* effect of a gene may be only a by-product of other important and essential physiological effects that it brings about. Hence any deductions based on the visible changes in the structure may be entirely misleading.

It is important not to forget that any haphazard change in a highly organized piece of machinery is likely to injure the machine. There must be comparatively few alterations that would improve the adaptive relation of such a system. Furthermore, changes are more likely to succeed if they affect some detail than if they cause sudden and great alterations, for even an extreme alteration, in itself beneficial when considered alone, may be injurious unless the rest of the organism is in harmony with it. It is no doubt this last consideration that is uppermost in the minds of those who contend that evolution must take place by slight advances in directions that do not throw the organism out of harmony in the delicate adjustments already acquired. It is true that many mutant changes are extreme ones and hence will be rejected in general competition, or indifferent, and hence have small chance of getting a foothold. It is, however, unfair to extend this consideration and infer that no mutations will be advantageous. In fact, unless evolution is directed by mysterious Unknown Agents along adaptive lines, by Unknown-chemical-elements, *i. e.*, by some Bion, the chance that any random change will be disadvantageous is inevitable, regardless of whether variations are due to mutations or to some other sort of change. If past competition has raised living species to a high point of efficiency in the environment in which they maintain themselves, the expectation of improvement through any one random change must be very small.

Some at least of the differences of opinion between the mutationist and the systematist may be traced to the above sources. There are also other grounds of disagreement: (1) The fact, for instance, that most of the characters studied by mutationists appear to be deficiencies has prejudiced students of evolution against these characters as a class. (2) The fact that most of the mutant types as well as many of the domesticated animals and cultivated plants can survive only under the artificial conditions of man's care may appear to put them all out of court when comparisons are made with wild types. (3) The fact that many of the mutant characters of domesticated forms are recessive has been supposed to count against their consideration as factors in evolution.

These "facts" undoubtedly call for consideration. Let us attempt to give them their full value and see if they really invalidate the view of the mutationist who believes that the mutations that he meets with throw light on what kinds of variations contribute to evolution.

In answer to the first (1) objection, that many mutant types are deficient, *i. e.*, less complicated, it should be pointed out that the objection would hold only if all mutants were deficiencies. This is not the case, for some of them are actual additions or further developments of the original structures. No one would pretend to maintain that the majority of mutant changes have a survival value. But mutationists do think that mutant changes having a survival value arise in the same way as do others that have no such value; for, they can point to actual cases where such mutants have survived and replaced the original type, and they have found no evidence that supports the view that useful and useless characters arise in entirely different ways. The opponents of the mutation theory have occasionally tried to make it appear that mutationists believe that most of the deficient mutant types that they study represent, or might represent, possible stages in the evolutionary process. I do not know of a single advocate of such a view—it is palpably absurd.

The second objection, viz., that mutant types survive only under domestication, has really no bearing on the question unless it could be shown that all mutant characters are unfitted for survival. As a matter of fact, numerous cases are on record where mutant differences characterize wild races and species of animals and plants.

The third objection is more difficult to meet because the relation of dominance to recessiveness is always a relative matter,

and also largely a matter of definition. The following considerations have nevertheless a bearing on the supposed difficulty: (*a*) Dominant mutants, if they introduce an advantageous change, have a better chance of survival than recessive ones equally endowed, because the individual that carries the dominant gene has the immediate survival advantage that the character endows it with. (*b*) Since it appears that a large proportion of mutant types are recessive, the chance, that any wild type gene that occurs has arisen as a recessive mutation is increased. (*c*) After genes have been incorporated in the wild type there is no way of knowing whether they arose as a dominant or as a recessive mutation. That they may later be more likely to produce new genes recessive to them is not an argument that they themselves arose as dominants.

There is a further consideration to be noted in the above connection. It is not true that most dominants are superior to the wild type from which they arose. Several known dominant mutants are no better off than other recessive mutants, conversely some new recessive mutants have a higher survival value than some of the new dominants. It is questionable whether dominant mutants as a class are better endowed for survival than recessives.

In conclusion, then, it appears that the objection to recessives is based on the ground that they are mutants rather than that they are recessives.

There still remains a further highly theoretical consideration that may be briefly referred to in this connection. Why so many new mutations should be recessive is admittedly a problem for which we have no solution. It will not suffice to state that the wild type will probably be more stable if the mutant is a dominant, for, so far as we know, the stability of a gene has nothing to do with its dominance. There is evidence that the mutant gene is as stable, in the sense that it is no more likely to mutate again, as is the allelomorphic gene representing the wild type. Suppose, however, that the wild-type gene is a highly complex compound or molecule. It seems plausible to assume that disintegrative changes would be more likely to occur than changes that build it up into higher stages of complexity. Suppose, further, that degradation (loss of complexity) carries with it the likelihood that the character itself is less highly specialized, or developed, or conspicuous (any vague phrase will suffice), it may then appear reasonable that the more highly specialized end product will be the furthest reached

and hence dominate the product derived from any degraded stage.[3] Such considerations are highly speculative at the present stage of genetic work and we lack entirely evidence that can give them any special weight. For the present it is better, I think, to leave such difficulties in abeyance. It is, however, not improbable that we may gain some light on this question when we come to know more about the relations of mutant dominant genes to the wild type gene, from which they are derived. Already some important facts have come to light in the behavior of the gene for Bar eyes in *Drosophila*, as shown by Zeleny and May.

It should not pass unnoticed that the preceding discussion takes for granted, by implication at least, that new genes do not appear; in a word, that the most primitive organism had the same number of genes as have the more highly evolved animals and plants. Bateson has shown where the assumption that all new genes are losses of old ones leads. But the opposite point of view is tenable, viz., that new genes arise during evolution, and even that evolution is due to their appearance. How new genes could arise is unknown—whether by a splitting process within the chain of old ones, or by doubling of chromosomes, or duplication of parts of chromosomes, or out of some less specialized substratum in which the existing genes are embedded. If the mutations that we study are really only degradation products (losses if one prefers) of genes that have arisen in a different way during the evolutionary process, it might still be conceded that they are useful in recombination which may be one, even though it may not seem to be the most important, phenomenon of evolution.

It is true that practically all the genes we know anything about are transmitted according to Mendel's laws, and it is only genes so transmitted that are involved in heredity, except in the few cases of plastid transmission. If, then, it should be claimed that evolutionary genes arise in a different way from Mendelian genes, it must be granted that the former behave as partners to the latter in the same way as the latter behave as partners to each other when they meet, as in the case of mul-

[3] Bateson, arguing from character to gene, has suggested that the mosaic distribution of color, for example, is due to a fractionation of the gene. The speculation above has only a remote resemblance to this view. There need be no relation whatsoever between the nature of the change in the gene and the way in which its effects are distributed except that, as here suggested, degradation of the gene may weaken the extent to which some end stage or part of that end stage is realized. For dilution effects the two views are not so obviously different.

tiple allelomorphs. Such a relation can not, however, be used to establish the identity of the two suppositious classes of genes. We must search elsewhere for evidence bearing on this important question.

MUTANT SPECIES AND UNIT CHARACTERS

In his original definition of the Mutation Theory, De Vries regarded the change, however slight, as one that was far-reaching, producing an individual that was something new throughout. He compared the mutant types to the small species of Draba verna or to other polymorphic groups familiar to botanists. The Mendelian work led at first to a somewhat different conception of the change involved in a single mutation. The emphasis was laid on "unit characters," so-called. It was generally implied that a mutation in the germ plasm led to a change in some particular organ of the body, *i. e.*, its effects were localized, not general. During the seventeen years that have elapsed since De Vries's formulation it has become apparent that the more familiar we are with a given form the more changes we can generally recognize associated with a single mutation, although it is also true that in many cases some one organ often shows the effects more conspicuously, and this organ is chosen as a matter of convenience as the earmark of mutation. On the whole, the evidence has made it clear that De Vries was more nearly right in his diagnosis. The more extreme claim would be that a change in any gene in the germ plasm affects all parts of the resulting individual. The opposite claim would be that a change in the members of a pair of genes affects only a particular part of the body, thus identifying "unit changes" in the germ plasm with "unit characters" in the individual. The evidence that we now have shows that in most cases at least neither extreme statement corresponds with the facts, but that while the particular genes often produce their most marked effects on certain regions or organs of the body, yet it is no less important to recognize the widespread effects of mutant genes. Any attempt to identify the nature of the gene from the changes it produces in one organ can not safely ignore its other effects in other organs. If the products of a gene do not act on a particular organ in its final stage, but through a chain of reactions in the embryo, we should expect more than a single kind of effect.

If, as just stated, each gene may affect several parts of the body, it follows with some probability that the same part may

be affected by several genes. A similar conclusion is reached in another way. There are many mutants that show differences in the same organ, each difference dependent on a different gene. In the fruit fly, for instance, there are about 50 different eye colors, 15 body colors and many races with wings of different length, shape and breadth. It is probable that at least several, perhaps all, of the normal allelomorphs (genes) of the eye colors may also take part in the formation of the eye color in the sense that they all take part in building up the body, and the end result is modified according to the substratum that they have produced. Carried to an extreme the view might mean that every part of the body is influenced by the total of all the genes, which means, of course, the entire germ plasm. The conception is exactly the converse of the Roux-Weismann conception of the relation between the germ plasm and the end-product of its activity, which conceived each end result as the special product of one or a few particular genes. The statement sometimes made that the modern genetic conception of the gene is identical with that of Weismann is not even half true. What the two theories have in common is not peculiar to Weismann, viz., that the germ plasm is made up of discrete particles—a view held by Bonnet, Herbert Spencer, Darwin, Haeckel and several other naturalists—and what the two views do not have in common is the special relation between the gene and the character that Weismann, following Roux (who in turn goes back to Bonnet, not to trace the theory to the preformationists themselves), made one of the chief supports of his theory of development.

It is not necessary to advocate the extreme view mentioned above—that every part is influenced by the whole germ plasm. As yet our information is too meager to warrant such a wide generalization, yet speaking personally the view is more sympathetic to me than the one that limits the influence of each gene to a very few regions of the body. I incline more to the other side, because the embryological history of the individual shows that the differentiation of the organs is a gradual process through which successive stages are passed in building up the complicated end product. If each of the stages is under the influence of the hereditary material, any alteration at any stage in the building up might be expected to affect in some degree the end results.

This relation is somewhat similar to another relation, but the two should not be confused with each other A specific gene may be essential to the normal development of a certain organ,

which organ through an internal secretion may affect other parts of the body, or even the body "as a whole." If, for example, the development of the thyroid gland were known to be dependent on the presence of a certain kind of gene (amongst all of the others involved in its formation) a change in the postulated gene leading to the arrest in the development of the thyroid gland would, owing to the lack of a sufficient amount of some internal secretion of that gland, produce a malformed child with all of the various stigmata of the cretin. The conclusion that the gene ultimately produces its effect on the body by means of an internal secretion, here thyroidin, does not mean that the gene itself is thyroidin. It is conceivable that it may be, but such an assumption is not a necessary deduction from the evidence, and is not needed for the logical interpretation of the results. We hope of course some day to discover the nature of the materials that we call genes and the way in which they affect the developmental process, but in the meantime the distribution of the materials of the germ plasm during the ripening of the eggs and sperm is the center of present interest to students of Mendelian heredity. While I am aware that this statement may seem to take a too narrow view of the problems involved, separating as it does the mechanism of Mendelian heredity from the later physiological influences of the gene on embryonic development, it has proven in practise premature to base speculations as to the composition of the gene on the physiological processes that take place at some unknown stage in the development of the embryo even although these processes are admittedly due to the presence of a special gene.